Reactions of 4-methylidenedioxolan-2-ones with 2-methyltryptamines. Synthesis of core analogs of aurantioclavine

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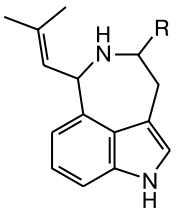
4-Hydroxy-4,5,5-trimethyl-3-[2-(2-methyl-7-R-1*H*-indol-3-yl)ethyl]-1,3-oxazolidin-2-ones (R = H or Alk), which were synthesized from 4-methylidene-1,3-dioxolan-2-one and substituted 2-methyltryptamines, undergo intramolecular amidoalkylation when treated with polyphosphoric acid. First representatives of a new heterocyclic system, *viz.*, oxazolo[3′,4′:1,2]azepino[5,4,3-*cd*]indole, which are core analogs of aurantioclavine, were prepared.

Key words: 4-methylidenedioxolan-2-ones, 2-methyltryptamines, 4-hydroxyoxazolidin-2-ones, intramolecular amidoalkylation, 6,7,11,11a-tetrahydro-4*H*-oxazolo[3′,4′:1,2]azepino[5,4,3-*cd*]indole, aurantioclavine.

Aurantioclavine (**1a**) and clavicipitic acid (**1b**) isolated from *Penicillium aurantio-virens*[1,2] and *Claviceps fusiformis* 139/2/1G,[2] respectively, as well as their numerous analogs have attracted recent attention due to their biological activities.[3,4]

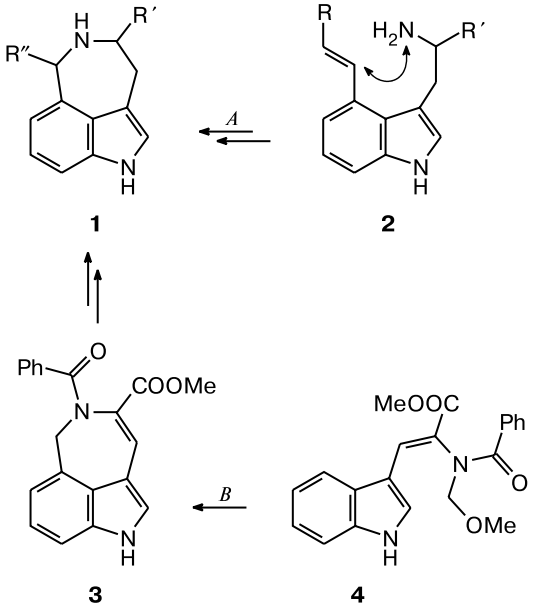


1a,b

R = H (**1a**), COOH (**1b**)

Several synthetic approaches were developed for the preparation of these compounds. As a rule, these procedures are based on difficultly accessible 4-substituted indole derivatives.[5,6] The general strategy of these methods, which consists in constructing system **1** from indoles **2**, is presented in Scheme 1 (path *A*).

Scheme 1



An approach to such structures by intramolecular amidoalkylation involving C(4) of the indole system (path *B*) was described only in one study,[7] where dihydroazepino[5,4,3-*cd*]indole derivative **3** was prepared by cyclization of enamide **4**.

The aim of the present study was to synthesize oxazolidin-2-one derivatives **7a—c**, which are condensation products of dioxolan-2-one **5** with 2-methyltryptamines **6a—c**, investigate their behavior under conditions of intramolecular amidoalkylation, and develop a new approach to the synthesis of azepino[5,4,3-*cd*]indoles.

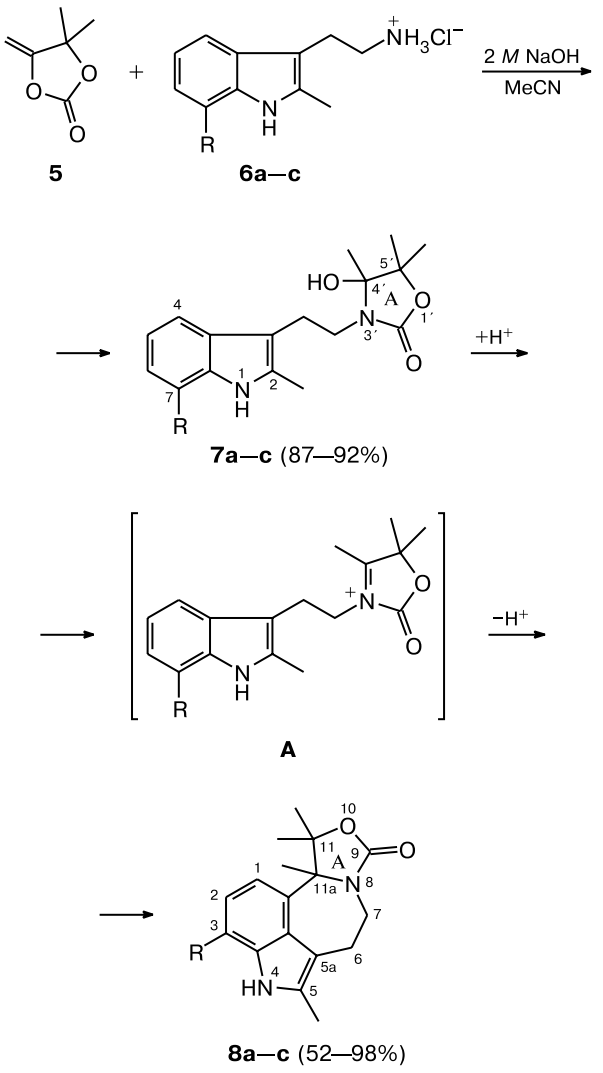
Earlier, we have demonstrated that *N*-(2-arylethyl)-4-hydroxyoxazolidin-2-ones, which were synthesized from 2-(3,4-dimethoxyphenyl)ethylamine and 5-substituted 4-methylidenedioxolan-2-ones, serve as sources of acyliminium ions under conditions of intramolecular amidoalkylation. The latter react with different nucleophiles. In these reactions, the benzene ring activated with respect to the nucleophilic attack serves as a nucleophile

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 542—545, March, 2004.

resulting in the closure of oxazolo[4,3-*a*]isoquinolin-3-ones.[8]

It is known[9] that the electrophilic substitution can occur in the benzene ring in compounds containing a substituent at position 2 of indole. Hence, the attack of the acyliminium species at position 4 of compounds **7a—c** can lead to the closure of the azepinoindole system (Scheme 2).

Scheme 2



5 **6a—c**

7a—c (87—92%)

A

8a—c (52—98%)

R = H (**a**), Me (**b**), Et (**c**)

Oxazolidinones **7a,b** were prepared at room temperature in high yields. The ^{1}H NMR spectra of these oxazolidinones show signals for the OH group (δ 5.34—5.81), the —CH_2—CH_2— fragment, the Me groups, and the NH group of indole. The mass spectra of these compounds have molecular ion peaks. Dehydration giving rise to the $[M - 18]^+$ ion is a characteristic fragmentation pathway.

The reaction of 7-ethyl-2-methyltryptamine did not afford compound **7c**; instead, its dehydration product **7c´** was prepared (according to ^{1}H NMR spectroscopic data) in 87% yield (R_f = 0.83). The ^{1}H NMR spectrum (δ, *J*/Hz) of this compound has the following signals: 1.43 (t, 3 H, $CH_2\underline{Me}$), 1.50 (s, 6 H, 2 Me), 2.50 (s, 3 H, $C(2)\underline{Me}_{ind}$), 2.87 (q, 2 H, $C\underline{H}_2Me$), 3.07 and 3.68 (both t, 4 H, CH_2CH_2), 4.00 and 4.20 (both d, 2 H, $=CH_2$, *J* = 1.1 Hz); aromatic protons: 7.00 (d, 1 H, *J* = 7.7 Hz), 7.10 (t, 1 H), 7.45 (d, 1 H, *J* = 7.7 Hz); 7.80 (br.s, 1 H, NH). The mass spectrum of **7c** has the corresponding molecular ion peak. The problem of dehydration of oxazolidinones has been discussed in-depth elsewhere.[10]

The IR spectra of all the compounds synthesized show an absorption band of the C=O group.

Compounds **7** melt over a rather wide temperature range, which is apparently associated with partial dehydration. Therefore, we did not perform elemental analysis of these compounds.

Compounds **7a,b,c´** underwent intramolecular amidoalkylation when treated with polyphosphoric acid. At room temperature (TLC data), only partial dehydration of compounds **7a,b** ocurred, whereas compound **7c´** remained unchanged. Heating of the reactions mixtures at 100 °C for 4—8 h led (TLC data) to the disappearance of the starting products and formation of intramolecular amidoalkylation products.

We believe that acyliminium species **A**, which is generated from the oxazolidin-2-one ring under the reaction conditions (see Scheme 2), attacks position 4 of indole to form the tetrahydroazepine ring giving rise to derivatives of a new heterocyclic system, *viz.*, oxazolo[3´,4´:1,2]azepino[5,4,3-*cd*]indole **8**.

The ^{1}H NMR spectra of compounds **8a—c** have neither signals for the protons of the hydroxy group nor signals of the $=CH_2$ group. The overall integral intensity of the signals for the aromatic protons is a unity smaller than that in the spectra of the starting compounds **7a,b,c´**. For example, the ^{13}C NMR spectrum recorded for compound **8a** using the DEPT technique has signals for only three CH_{arom} carbon atoms. The ^{1}H NMR spectra of all the compounds synthesized show a signal of the NH group of indole. The signal of the methyl group at position 4´ of the starting oxazolidinones is always observed at lower field compared to that in the spectra of the final azepinoindoles ($\Delta\delta_{av} = -0.83$). Apparently, this is associated with the fact that the methyl group in cyclic structure **8** experiences the anisotropic effect of the indole system. The mass spectra of compounds **8a—c** each have molecular ion peaks. The fragmentation of the molecular ion is characterized by abstraction of the Me group to form the $[M - 15]^+$ ion followed by elimination of the CO_2 mol-

ecule giving rise to the $[M - 15 - 44]^+$ ion. These facts provide convincing evidence that the acyliminium species attacks position 4 of indole to form azepinoindole structure **8**.

This direction of cyclization and high yields of the final products are attributable to two main reasons. First, the attack cannot occur at the substituted position 2 of indole. Second, the attack at position 3 should lead to the *endo-trig* process, which is generally unfavorable in the case of formation of five-membered rings.[1]

It should be noted that cyclization of compound **7b** afforded compound **8b** in substantially lower yield compared to those obtained in other reactions. This is a rather unusual fact, because the Me group at position 7 of indole does not create steric hindrance to the attack of the acyliminium species at position 4 and even should facilitate the electrophilic substitution due to $+I$ and $+M$ effects. An analogous effect was not observed in the synthesis of compound **8c** from compound **7c´** containing the ethyl substituent at position 7.

Hydrolytic cleavage of the oxazolidinone ring in amidoalkylation products and subsequent dehydration of the β-amino alcohol that formed should lead to analogs of aurantioclavine **1a**, *viz.*, 6-isopropenyl-6-methylazepinoindoles, which have previously been difficultly accessible.

The approach under consideration differs from the previously known methods for the azepine-ring closure used in the synthesis of azepino[5,4,3-*cd*]indoles and allows one to vary substituents in the indole fragment over a much wider range. In the present study, we restrict our consideration to cyclization of oxazolidin-2-ones, which were prepared from unsubstituted 2-methyltryptamine or its 7-alkyl-substituted analogs. In the future, we plan to examine the influence of substituents both in tryptamine and starting dioxolan-2-one on the cyclization path in more detail.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker DRX 500 instrument operating at 500.13 MHz using a signal of the nondeuterated solvent as the internal standard. The IR spectra were measured on a Perkin—Elmer 577 instrument (in KBr pellets). The mass spectra were obtained on an MS-30 instrument (Kratos) with direct inlet of the sample into the ion source; the energy of ionizing electrons was 70 eV; the temperature of the ionization chamber was 250 °C. The constants and yields of the compounds synthesized are given in Table 1. The ^{1}H NMR spectroscopic data are listed in Table 2. Thin-layer chromatography was carried out on Silufol UV_{254} plates in a 1 : 1 benzene—ethyl acetate mixture. The starting 2-methyltryptamine hydrochlorides were prepared according to a procedure described earlier.[12]

4-Hydroxy-4-methyl-3-[2-(2-methyl-1*H*-indol-3-yl)ethyl]-1,3-oxazolidin-2-ones (7a,b) (general procedure). A solution of methylidenedioxolan-2-one (**5**) (2.691 g, 0.021 mol) in MeCN (10 mL) was added to a mixture of the corresponding 2-methyltryptamine (0.02 mol) and 2 *M* NaOH (10 mL) in MeCN (10 mL). The reaction mixture was stirred for 48 h. The solvent was distilled off under reduced pressure. The residue was successively washed with a 4 : 1 Et_2O—*n*-hexane mixture (2×5 mL) and water (3×10 mL).

5,11,11,11a-Tetramethyl-6,7,11,11a-tetrahydro-4*H*-oxazolo[3´,4´:1,2]azepino[5,4,3-*cd*]indoles (8a—c) (general procedure). Oxazolidinone **7a,b,c´** (0.01 mol) was added portionwise to a tenfold excess (by weight) of polyphosphoric acid heated to 100 °C. The reaction mixture was stirred for 4—8 h (TLC control) at this temperature. Then the reaction mixture was cooled and cold water (100 mL) was added. The precipitate that formed was filtered off and washed with water to the neutral reaction.

Table 1. Constants and yields of compounds **7a,b** and **8a—c**

Compound	R_f	M.p. /°C	Yield (%)	Found / Calculated (%)			Molecular formula	IR spectrum, $\nu_{C=O}$/cm^{-1}	MS, m/z (I_{rel} (%))
				C	H	N			
7a	0.53	164—167	92	—	—	—	—	1728	302 $[M]^+$ (3.4), 284 $[M - H_2O]^+$ (13.6), 157 (39.4), 144 (100), 115 (3.2)
7b	0.55	151—155	87	—	—	—	—	1726	316 $[M]^+$ (0.5), 298 $[M - H_2O]^+$ (10.1), 171 (25.5), 158 (100), 143 (4.8)
8a	0.64	>300 (DMF)	98	71.59 / 71.81	7.14 / 7.09	9.79 / 9.85	$C_{17}H_{20}N_2O_2$	1720	284 $[M]^+$ (40.4), 269 $[M - Me]^+$ (46.8), 225 $[M - Me - CO_2]^+$ (24.2), 198 (100), 183 (45.2)
8b	0.66	284—286 (decomp.)	52*	72.24 / 72.46	7.50 / 7.43	9.22 / 9.39	$C_{18}H_{22}N_2O_2$	1716	298 $[M]^+$ (30.6), 283 $[M - Me]^+$ (55.3), 239 $[M - Me - CO_2]^+$ (22.3), 212 (100), 197 (47.0)
8c	0.67	261—262 (decomp.)	89	72.82 / 73.05	7.80 / 7.74	8.82 / 8.97	$C_{19}H_{24}N_2O_2$	1728	312 $[M]^+$ (42.5), 297 $[M - Me]^+$ (67.1), 253 $[M - Me - CO_2]^+$ (11.7), 226 (100), 211 (35.9)

* The yield is given with respect to the starting tryptamine hydrochloride.

Table 2. ^{1}H NMR spectra of compounds **7a,b** and **8a—c** (DMSO-d_6, δ, *J*/Hz)

Compound	Ring A		—CH_2—CH_2—	H_{Ar}	NH (br.s)	Me (s)	Other signals
	Me_2 (both s)	Me (s)					
7a	1.12, 1.16 (5′,5′-Me_2)	1.27 (4′-Me)	2.73 (t, 2 H, *J* = 8.2); 3.09—3.15 (m, 1 H); 3.22—3.30 (m, 1 H)	6.81 (d, 1 H, *J* = 7.9); 7.22—7.34 (m, 2 H); 7.51 (d, 1 H, *J* = 7.9)	10.47	2.35 (2-Me)	5.61 (s, 1 H, OH)
7b	1.11, 1.16 (5′,5′-Me_2)	1.29 (4′-Me)	2.88 (t, *J* = 8.2, 2 H); 3.12—3.19 (m, 1 H); 3.20—3.28 (m, 1 H)	6.76 (d, 1 H, *J* = 7.1); 6.84 (t, 1 H, *J* = 7.1); 7.25 (d, 1 H, *J* = 7.1)	10.48	2.37, 2.43 (2-Me)	5.77 (s, 1 H, OH)
8a	1.58, 1.59 (11,11-Me_2)	0.71 (11a-Me)	2.74 (t, 1 H); 2.85 (d, 1 H); 3.22—3.34 (m, 1 H); 3.89—3.99 (m, 1 H)	6.78 (d, 1 H, *J* = 7.2); 6.96 (br.t, 1 H, *J* = 7.2, *J* = 7.8); 7.18 (d, 1 H, *J* = 7.8)	10.82	2.31 (5-Me)	—
8b	1.56, 1.57 (11,11-Me_2)	0.69 (11a-Me)	2.72 (t, 1 H); 2.84 (d, 1 H); 3.23 (t, 1 H); 3.92 (d, 1 H)	6.67 (d, 1 H, *J* = 7.3); 6.74 (d, 1 H, *J* = 7.3)	10.68	2.27, 2.34 (both s, 3,5-Me_2)	
8c	1.53, 1.54 (11,11-Me_2)	0.68 (11a-Me)	2.68—2.85 (m, 4 H); 3.26 (t, 1 H); 3.97 (d, 1 H)	6.72 (d, 1 H, *J* = 7.7); 6.81 (d, 1 H, *J* = 7.7)	10.69	2.27 (5-Me)	1.22 (t, 3 H, CH_2—Me, *J* = 13.4)*

* The signals of the CH_2 group of the ethyl substituent overlap with the signals of one of the CH_2 groups of the tryptamine fragment and appear as a multiplet at δ 2.68—2.85 (4 H).

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Received December 30, 2003